REMARKS

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-3, 6-12 and 19-21 are pending in the application, with claim 1 being the sole independent claim. Claim 1 has been amended herein and claim 5 has been canceled. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

In Regard to the Rejection of Claims 1-3, 5-12 and 19-21 Under 35 U.S.C. § 112

Claims 1-3, 5-12 and 19-21 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner has asserted that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Office Action, page 2, lines 8-12. Applicant respectfully traverses the rejection.

Claim 1 as amended in the Response filed March 7, 2008, specifies that the buffer solution is an acetate buffer solution containing 0.044 to 15 mM acetate or a citrate buffer solution containing 3.87 mM or less citrate. However, the Examiner has suggested that present application only provides support for sodium acetate trihydrate at levels between 0.00006-0.2% - not acetate levels per se. Similarly, the Examiner has suggested that the application only provides support for citrate at 3.87 mM.

In response, claim 1 has been amended herein to specify that the buffer solution is an acetate buffer solution having an acetate concentration of about 4.5 – 8.5 mM. Furthermore, claim 5 has been canceled.

Support for an acetate buffer solution having an acetate concentration of about 4.5 – 8.5 mM can be found, for example, at page 7, lines 1 – 3, original claim 5, and in Examples 1

– 5 and 7, which include the use of a buffer containing 4.8 mM acetate as the buffering agent. As would be readily appreciated by one of skill in the art, the buffering agent in the sodium acetate trihydrate solutions used in the Examples of this application include acetate as the buffering agent; the sodium and the trihydrate do not act as buffering agents. Accordingly, the present application provides support for any acetate-containing buffer solution having the recited acetate concentration and, in our view, the claims should not be limited to a particular acetate salt.

Therefore, as the rejection to claims 1-3, 6-12 and 19-21 has been rendered moot, Applicant respectfully requests that the rejection of these claims under 35 U.S.C. § 112, second paragraph, be withdrawn.

In Regard to the Rejection of Claims 1-3, 5-12 and 19-21 Under 35 U.S.C. § 103(a)

The Examiner has rejected of claims 1 – 3, 5 – 12 and 19 – 21 under 35 U.S.C. § 103(a) as being unpatentable over Asmus *et al.*("Asmus") and Watson *et al.* ("Watson") and the Practical Engineering website reference ("website") in view of the FDA Inactive Ingredient list, (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm; "Inactive Ingredient list") and ScienceLab.com, Material Safety Data Sheet: Sodium Acetate MSDS ("MSDS"). Applicants respectfully traverse this rejection.

Asmus teaches that solutions of methacholine buffered at a pH of approximately 8.3 are stable when stored frozen. These solutions were found to be unstable at room temperature. Asmus suggests the use of slightly acidic pH to stabilize methacholine chloride in solution. However, nowhere in Asmus is there any teaching or suggestion of stable methacholine chloride solutions comprising acetate at any concentration, or having a pH of between 4 and 5.

Watson discloses that methacholine chloride solutions undergo hydrolysis if the pH exceeds 6. In support of this statement, Watson tested methacholine solutions having a pH of 4, 5 and 6. There is no distinction made in Watson as to any improved stability observed in solutions having a pH in the range of 4 to 5. There is no distinction made in Watson as to any improved stability (in terms of potency and pH profile) observed in solutions buffered using acetate. Furthermore, nowhere in Watson is there any teaching or suggestion of the use of acetate buffer having the recited acetate concentration.

The website teaches a process for sterilizing liquid products comprising aseptic processing and filtration that can be used for liquid pharmaceuticals not amenable to thermal sterilization.

The Inactive Ingredient list teaches that the sodium citrate maximum level in a solution for inhalation is 0.6%. Sodium acetate is not listed as an inactive ingredient used in solutions for inhalation

The MSDS for sodium acetate teaches that sodium acetate in solution is a respiratory irritant.

The Examiner has suggested that one of ordinary skill in the art would have been motivated to combine the above references and to make an inhalable solution of methacholine in a buffer solution comprising acetate or citrate in levels that are within the FDA approved levels. In responding to the Applicant's previous arguments, the Examiner has further suggested that one of ordinary skill in the art would have been motivated to decrease the amounts of acetate or citrate levels in the old composition to make a composition having levels of buffering agent within pharmaceutically acceptable levels.

Applicant maintains their previous position that one of skill in the art would not have been so motivated. It was clear from the prior art that maintaining pH of methacholine solutions below 6 was important for stability. Buffering agents were used to keep pH below 6. However, one of skill in the art having regard to the prior art could not have known or expected that a lower concentration of buffering agent would be successful in maintaining pH of a methacholine solution below 6 (let alone within the recited range of from 4 to 5), particularly in view of the fact that methacholine degradation in solution causes pH to increase.

Nonetheless, in order to advance prosecution of the present application, Applicant has amended claim 1 to specify that the claimed inhalable methacholine chloride solution includes an acetate buffer solution having a pH in the range of 4 to 5 and an acetate concentration of about 4.5 – 8.5 mM.

One of skill in the art having regard to Watson, Asmus, the website and the Inactive Ingredient Guide, and in view of the MSDS for sodium acetate would not have had any reason to expect an acetate buffer having a pH in the range of 4 to 5 and an acetate

concentration of about 4.5 – 8.5 mM to be successful in stabilizing solutions over the range of methacholine chloride concentrations recited and in providing inhalable solutions. The success of the acetate buffer in stabilizing the methacholine solutions is demonstrated by the pH and potency stability of the formulations of the present invention (See, for example, Tables 9 – 26), even under accelerated storage conditions.

Furthermore, despite the information provided in the MSDS regarding the respiratory irritation caused by inhalation of sodium acetate solutions and the fact that sodium acetate is not included in the Inactive Ingredient guide as a reagent used in inhalable products, the data provided in Example 7 (at pages 36 and 39) demonstrate that an acetate diluent (0.066% sodium acetate trihydrate) produced the same response in FEV_1 as a saline diluent. The pH of the acetate diluent in this study was not adjusted to within between 4 to 5 since methacholine stability was not a concern. This data demonstrates that acetate solutions having concentration within the presently claimed range can be used successful in a solution for inhalation.

These combined unexpected results demonstrating stability and suitability for inhalation serve to overcome any basis for *prima facie* obviousness that the Examiner may assert.

Asmus supports the finding of Watson that a buffer is preferred for storage of methacholine solutions, but makes use of a buffer solution including 0.275% sodium bicarbonate and 0.4% phenol. Thus, Asmus does not provide the skilled worker with any reason to use an acetate buffers at all, let alone at the presently recited concentration of from about 4.5 to 8.5 mM acetate. Furthermore, the claims of the present application are limited to formulations containing an acetate buffer solution having a pH of between 4 and 5. Neither Asmus nor Watson teach or suggest that this is the appropriate pH range for stable methacholine formulations.

The data provided in Example 1 of the present application, and in particular, the accelerated stability data (40°C) shown in Tables 5 – 8, clearly demonstrates that the buffer solutions having pH in the narrow range of from 4 to 5 provides superior stability in comparison to the buffer solution at pH 6.

The data provided in Example 2 demonstrates that acetate buffer at pH 4 has superior buffering capacity to citrate buffer at pH 5 and that the acetate buffer was better than the citrate buffer in stabilizing methacholine chloride at the lower concentration. In particular, the Applicant respectfully draws the Examiner's attention to the accelerated data provided in Tables 9 and 10. The data provided in Example 4 further demonstrates that acetate buffer at pH 4 and at pH 4.5 has superior buffering capacity to citrate buffer at pH 5 (see, in particular, Tables 12 – 14). As would be well appreciated by one skilled in the art, the ability of the acetate buffer to maintain a relatively constant pH over time, even under accelerated conditions and in the presence of a higher concentration of methacholine chloride, is a desirable feature for pharmaceutical products.

In contrast to the foregoing, Watson discloses compositions comprising methacholine in various buffer solutions, including acetate and citrate buffers. The data in Watson merely suggests that the buffer solution should have a pH of at least 6. Asmus discloses formulations of methacholine in a buffered saline solution containing phenol and having pH of approximately 8.3 (see, page 1635, column 1, line 3). Thus, nowhere in Watson or Asmus is it taught or suggested that the buffer solution is preferably acetate at a concentration of from about 4.5 to 8.5 mM or that the pH of the buffer solution in the stable methacholine formulations should be between 4 and 5.

The additionally cited website, Inactive Ingredient list and MSDS do not overcome the deficiencies of Asmus and Watson. Therefore, claim 1 is believed to be allowable.

Dependent claims 2, 3, 5 – 12 and 19 – 21 recite additional features of the invention and are therefore believed to be allowable for the same reasons recited above with respect to claim 1 and for the additional features recited therein.

Accordingly, Applicant respectfully requests that the rejections of the claims under 35 U.S.C. § 103(a) be withdrawn.

In view of the above amendments and remarks, the Applicant respectfully submits that all of the currently pending claims are allowable and that the entire application is in condition for allowance.

Should the Examiner believe that anything further is desirable to place the application in a better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number listed below.

At the time of filing of the present response, the Office was authorized to charge the fees believed to be necessary to a credit card. In case of any under- or over-payment or should any additional fee be otherwise necessary, the Office is hereby authorized to credit or debit (as the case may be) Deposit Account number 502977.

Respectfully submitted,

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